POSTER
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Durable efficacy of zenocutuzumab, a HER2 × HER3 bispecific antibody, in advanced *NRG1* fusion–positive (NRG1+) pancreatic ductal adenocarcinoma (PDAC)

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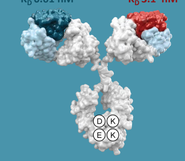
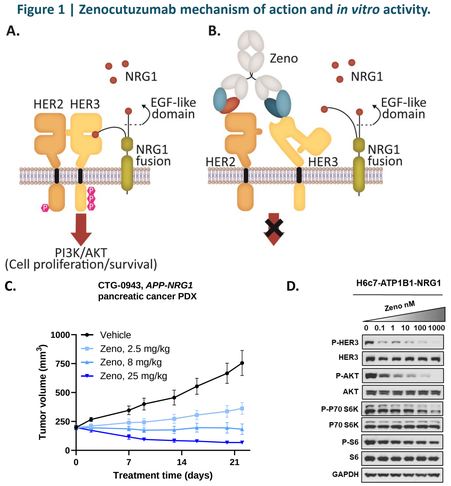


INTRODUCTION

- Neuregulin 1 (NRG1) is a ligand that binds to human epidermal growth factor receptor (HER) 3, and promotes HER2/HER3 heterodimerization and oncogenesis, leading to tumor growth.[1,2]
- Chromosomal rearrangements (fusions) involving *NRG1* are rare oncogenic drivers in a broad range of solid tumors, including pancreatic ductal adenocarcinoma (PDAC).[3,4] *NRG1* fusions are optimally detected with the use of RNA-based next-generation sequencing.[5]
- There are no approved therapies specific for *NRG1* fusion–positive (NRG1+) cancer; patients are treated according to standard of care for the underlying tumor type. Patients with advanced or metastatic NRG1+ PDAC that has progressed after standard therapy have a poor prognosis and limited therapeutic options.[6-8]
- Zenocutuzumab (MCLA-128) is a bispecific antibody that binds to the extracellular domains of HER2 and HER3 (**Figure 1**).[9]
  - Zenocutuzumab demonstrated efficacy in *in vivo* and *in vitro* NRG1+ cancer models across histologies.[10]
  - Anticancer activity is due to blocking NRG1:HER3 binding and HER2:HER3 dimerization, resulting in suppression of tumor cell proliferation and survival through the PI3K-AKT-mTOR oncogenic signaling pathway.[9,10]
  - *In vitro*, zenocutuzumab mediates antibody-dependent cellular cytotoxicity, eliminating tumor cells.[9,10]
- Zenocutuzumab was recently granted Breakthrough Therapy Designations for NRG1+ NSCLC and NRG1+ pancreatic cancer.
- Efficacy and safety of zenocutuzumab are being evaluated in patients with advanced NRG1+ cancer in the ongoing, pivotal, phase 2 eNRGy trial and early access program (EAP). Data are presented for patients with NRG1+ PDAC; data for patients with NRG1+ non-small cell lung cancer (NSCLC) were presented in a Mini Oral Session (**Presentation No. 1315MO**).

Figure 1 | Zenocutuzumab mechanism of action and *in vitro* activity.

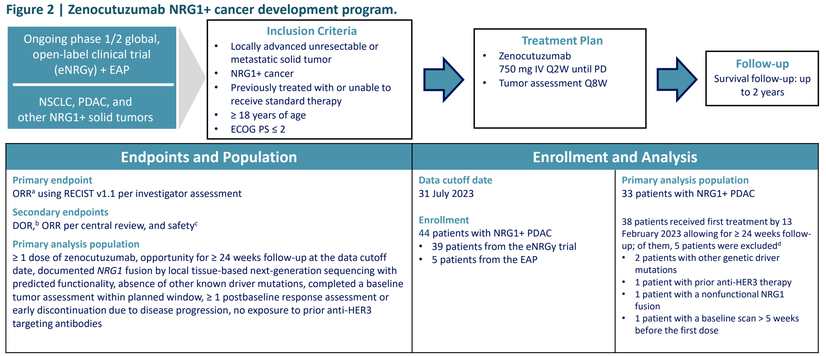


EGF: epidermal growth factor; HER: human epidermal growth factor receptor; NRG1: neuregulin 1; Zeno: zenocutuzumab; PDX: patient-derived xenograft.
(A) NRG1 fusion proteins function as ligands for HER3 (similar to NRG1) and bind to HER3 with high affinity to promote HER2/HER3 dimerization and downstream signaling. **(B)** Zenocutuzumab inhibits the NRG1/HER3 interaction via a "Dock & Block^{BX}" mechanism, where 1 arm of the antibody binds to the HER2 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and prevent HER2/HER3 dimerization. **(C)** NRG1+ pancreatic cancer PDX models treated with zenocutuzumab show inhibition of tumor growth and **(D)** inhibition of phosphorylation of HER3 and AKT.
Figure 1A and 1B adapted from Geuijen CAW, et al. *Cancer Cell*. 2018;33(5):922-936. Figure 1C and 1D adapted from Schram AM, et al. *Cancer Discov*. 2022;12(5):1233-1247.

TRIAL DESIGN AND OBJECTIVES

- The eNRGy trial (ClinicalTrials.gov Identifier: NCT02912949) is an ongoing, phase 1/2, global, open-label, multicenter trial in adult patients with advanced or metastatic NRG1+ solid tumors, including NRG1+ PDAC (**Figure 2**).
- A concurrent EAP (ClinicalTrials.gov Identifier: NCT04100694) is ongoing and is aligned with the eNRGy trial for eligibility criteria, zenocutuzumab treatment, and efficacy and safety assessment.

Figure 2 | Zenocutuzumab NRG1+ cancer development program.



Endpoints and Population	Enrollment and Analysis	
Primary endpoint ORR[a] using RECIST v1.1 per investigator assessment **Secondary endpoints** DOR,[b] ORR per central review, and safety[c] **Primary analysis population** ≥ 1 dose of zenocutuzumab, opportunity for ≥ 24 weeks follow-up at the data cutoff date, documented *NRG1* fusion by local tissue-based next-generation sequencing with predicted functionality, absence of other known driver mutations, completed a baseline tumor assessment within planned window, ≥ 1 postbaseline response assessment or early discontinuation due to disease progression, no exposure to prior anti-HER3 targeting antibodies	**Data cutoff date** 31 July 2023 **Enrollment** 44 patients with NRG1+ PDAC • 39 patients from the eNRGy trial • 5 patients from the EAP	**Primary analysis population** 33 patients with NRG1+ PDAC 38 patients received first treatment by 13 February 2023 allowing for ≥ 24 weeks follow-up; of them, 5 patients were excluded[d] • 2 patients with other genetic driver mutations • 1 patient with prior anti-HER3 therapy • 1 patient with a nonfunctional NRG1 fusion • 1 patient with a baseline scan > 5 weeks before the first dose

AE: adverse event; CR: complete response; CTCAE: Common Terminology Criteria for Adverse Events; DOR: duration of response; EAP: early access program; ECOG PS: Eastern Cooperative Oncology Group performance status; HER: human epidermal growth factor receptor; IV: intravenous; MedDRA: *Medical Dictionary for Regulatory Activities*; NRG1: neuregulin 1; NSCLC: non-small cell lung cancer; ORR: overall response rate; PD: progressive disease; PDAC: pancreatic ductal adenocarcinoma; PR: partial response; Q2W: every 2 weeks; Q8W: every 8 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.
[a] Defined as the proportion of patients with a best confirmed response of CR or PR per RECIST v1.1.
[b] Defined as the time from the date of first CR or PR to the date of first PD or death due to trial indication.
[c] AEs were coded using MedDRA v25.0 and graded using CTCAE v4.03.
[d] Per the statistical analysis plan.

NRG1+ PDAC PATIENTS

- As of the data cutoff date of 31 July 2023, 33 of the 44 patients treated with zenocutuzumab were included in the primary efficacy population.
- Patient demographic and disease characteristics are shown in **Table 1**.
- Median age was 49 years (range, 21–72).
- All patients had metastatic disease with liver involvement.
- All tumors were *KRAS* wild-type.
- The most frequently detected fusion partner was *ATP1B1* (55%).
- Patients had a median of 2 prior systemic therapies (range, 0–5); 97% of patients had received prior FOLFIRINOX (53%) and/or gemcitabine/taxane-based therapy (78%).
- Median duration of exposure was 9.4 months (range, 1–34).
- Six (18%) patients remained on therapy at the data cutoff date. Among patients who had discontinued therapy, most (22/33 patients [67%]) had discontinued due to disease progression (radiological or clinical), including 2 patients who died. No patient withdrew due to an adverse event.

Table 1 | Demographic and baseline disease characteristics (efficacy population).

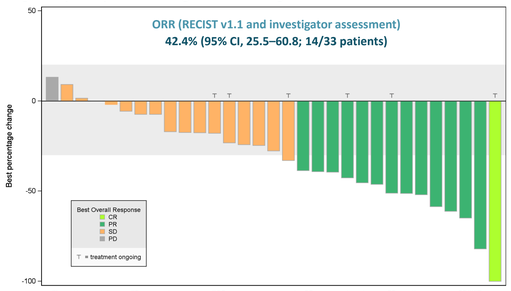
Characteristic	N = 33
Age in years, median (range)	49 (21–72)
Gender, male / female, n (%)	18 (55) / 15 (45)
Race, White / Asian / Other,[a] n (%)	28 (85) / 2 (6) / 3 (9)
ECOG PS, 0 / 1 / 2 / 3,[b] n (%)	18 (55) / 14 (42) / 0 / 1 (3)
KRAS wild-type, n (%)	33 (100)
Prior lines of systemic therapy, median (range)	2 (0–5)
Number of metastatic disease sites, median (range)	2 (1–8)
Metastatic disease site, liver / lung, n (%)	33 (100) / 10 (30)
NRG1 fusion partner, n (%)	
ATP1B1	18 (55)
SLC4A4 / *CD44* / *NOTCH2*	3 (9) each[c]
AGRN / *APP* / *CDH1* / *SDC4* / *THBS1* / *VTCN1*	1 (3) each[c]

EAP, early access program; ECOG PS: Eastern Cooperative Oncology Group performance status; *NRG1*: neuregulin 1; PS, performance status.
[a] Black or African American (n = 1), unknown (n = 1), missing (n = 1); [b] The patient with an ECOG PS of 3 had symptomatic ascites was enrolled in the EAP with the expectation of potential improved PS with treatment; [c] Value applies to each fusion partner listed in the row.

ANTI-TUMOR ACTIVITY IN NRG1+ PDAC

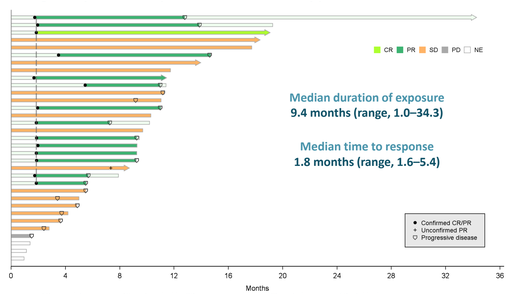
- The confirmed **overall response rate (ORR) was 42.4%** (95% CI, 25.5–60.8) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment:
  - 1 (3%) patient achieved a complete response, and 13 (39%) patients achieved a partial response (**Figure 3**).
  - 15 (45%) patients had stable disease (**Figure 3**).
  - Treatment is ongoing in 2 of 14 responders (14%; **Figure 4**).
- 27 of 33 patients **(82%) experienced tumor reduction** (**Figure 3**), and the clinical benefit rate was 72.7% (95% CI, 54-87).
- The median duration of response (DOR) was 9.1 months (95% CI, 5.5–12.0) by RECIST v1.1 per investigator assessment.
  - Kaplan–Meier estimate of the 6-month DOR rate was 71% (95% CI, 41–88; **Figure 5**).
- Of 27 evaluable patients, 21 (78%) showed a ≥ 50% decrease in CA 19-9 values from baseline (**Figure 6**).

Figure 3 | Best percent change in sum of target lesion diameter from baseline.[a]



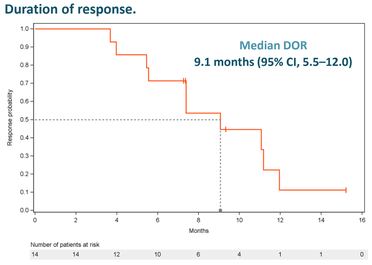
CI: confidence interval; CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease.
[a] Excludes 2 patients without a post baseline tumor assessment.
"T" indicates treatment is ongoing at the data cutoff date.

Figure 4 | Time to response and time on therapy.[a]



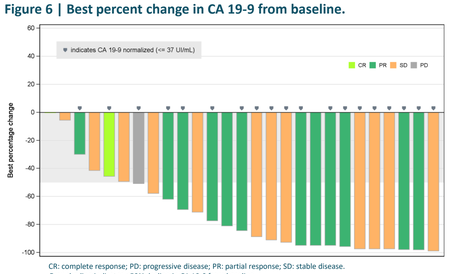
CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.
[a] Time on therapy is defined as treatment duration plus 2 weeks (with possible limitation from data cutoff date or death). Arrows indicate treatment is ongoing at the data cutoff date.

Figure 5 | Duration of response.



CI: confidence interval; DOR: duration of response.

Figure 6 | Best percent change in CA 19-9 from baseline.



CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease.
Gray shading indicates <50% decline in CA 19-9 from baseline.

SAFETY PROFILE

- Overall, a low incidence of grade 3 or 4 related treatment-emergent adverse events (TEAEs) was observed among all 189 NRG1+ cancer patients who received zenocutuzumab 750 mg Q2W monotherapy (**Table 2**).
- No patient discontinued zenocutuzumab due to related TEAEs.
- Infusion-related reactions[b] occurred in 23 of 189 (12%) patients, with no grade 3 or greater events.

Table 2 | Safety profile in NRG1+ cancer patients (N = 189).[a]

	Related TEAEs (≥10% and all Grades 3-4) n (%)		TEAEs irrespective of causality (≥10%) n (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
≥1 TEAE	115 (61)	11 (6)	166 (88)	66 (35)
Diarrhea	33 (17)	3 (2)	53 (28)	4 (2)
Infusion-related reactions[b]	23 (12)	0	23 (12)	0
Fatigue	18 (10)	0	30 (16)	4 (2)
Nausea	16 (8)	2 (1)	30 (16)	3 (2)
Vomiting	11 (6)	1 (1)	21 (11)	1 (1)
Anemia	7 (4)	1 (1)	29 (15)	7 (4)
Constipation	5 (3)	0	24 (13)	0
ALT increased	5 (3)	1 (1)	18 (10)	5 (3)
AST increased	5 (3)	2 (1)	14 (7)	5 (3)
Decreased appetite	5 (3)	1 (1)	16 (8)	2 (1)
Abdominal pain	3 (2)	1 (1)	21 (11)	4 (2)
Dyspnea	2 (1)	0	24 (13)	6 (3)
GGT increased	2 (1)	1 (1)	13 (6)	6 (3)
Platelet count decreased	2 (1)	1 (1)	4 (2)	1 (1)
Hyperuricemia	2 (1)	1 (1)	3 (2)	1 (1)
Bacteremia	1 (1)	1 (1)	2 (1)	2 (1)
Hypertransaminasemia	1 (1)	1 (1)	1 (1)	1 (1)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; EAP: early access program; GGT: gamma-glutamyltransferase; IV: intravenous; NRG1: neuregulin 1; PDAC: pancreatic ductal adenocarcinoma; Q2W: every 2 weeks; TEAE: treatment-emergent adverse event.
[a] Includes all patients with NRG1+ cancer treated with zenocutuzumab 750 mg IV Q2W in the eNRGy trial or EAP, including 44 patients with NRG1+ PDAC. [b]Composite term covering preferred terms considered by the investigator to be infusion-related reactions occurring within 24 hours of infusion start.

CONCLUSIONS

- **In this updated analysis, zenocutuzumab continues to demonstrate an unprecedented response rate, with robust durability in patients with previously treated metastatic NRG1+ PDAC.**
  - **ORR 42.4% (95% CI, 25.5–60.8; N = 33).**
  - **Median DOR 9.1 months (95% CI, 5.5–12.0).**
- **27 of 33 patients (82%) with NRG1+ PDAC treated with zenocutuzumab experienced tumor reduction.**
- **Zenocutuzumab demonstrated an extremely well tolerated safety profile, with only 6% of patients experiencing related grade 3-4 toxicities.**
- **Zenocutuzumab offers a potential new standard of care for patients with NRG1+ PDAC, a biomarker-driven rare entity with a significant unmet medical need.**

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